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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,349	06/05/2001	John C. Hiserodt	IRVN001DIV	8040

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/875,349	Applicant(s) HISERODT ET AL.	
	Examiner Christopher H Yaen	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-30 have been canceled with prejudice, claims 31-62 have been newly added. Therefore claims 31-62 are pending and examined on the merits.

Information Disclosure Statement

2. The Information Disclosure Statement filed 2/07/02 (paper no. 3) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112

3. Claims 31-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Regarding claims 31, 40-41, 45, 46, 55, 62, and dependent claims thereof, in the recitation of the phrases "associated with the cell outer membrane" or "membrane-associated", it is indefinite because it is unclear as to whether the cytokines are integral membrane proteins or whether the cytokines are bound to the surface of the cell.

5. Regarding claims 31, 38, 41 and dependent claims thereof in the recitation of the phrase "effective in treating neoplastic disease", it is indefinite because the final effect or effectiveness of the treatment is unknown (i.e. how much difference is needed to be considered effective). Also it is not clear what would constitute an effective treatment because the outcome to which is considered effective is not known.

6. Regarding claim 49 in the recitation of the phrase "a tumor associated antigen", it is unclear as to whether the TAA is part of a cell (i.e. expressed on the surface of the cell) or a naked antigen.

7. Regarding claim 34, in the recitation of the term "tumor", it is unclear as to the distinction between "tumor" and "cancer" recited in the claim.

8. Claims 31-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a cell expressing a mm-CSF cytokine associated with the outer cell membrase which generates an immunogenic response does not reasonably provide enablement for any composition comprising a cell expressing any cytokine associated with the cell outer membrane or for treating neoplastic disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. For the purposes of this rejection, the phrase "associated with the cell outer membrane" or "membrane associated", will be interpreted as meaning a cytokine that is linked to the outer membrane of a cell or is an integral membrane protein.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of

sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are drawn to a composition comprising a cell expressing a cytokine that is linked to the outer membrane of a cell or is an integral membrane protein, and a method of producing the composition, *supra*.

The state of the prior art and the predictability or lack thereof in the art: Currently, the art teaches that certain cytokines (M-CSF) are produced or expressed naturally on the surface of the cell (see Chen *et al* (Blood 2002; 100:1373-80)) and that such cytokines are important in the generating immunity. However, no art of record teaches the expression of any other cytokine to the surface of the cell or what effect such expression will have in terms of immunological response. The art also teaches that the transition from cell culture and in vivo mouse models to humans lack certain efficacy and is often unpredictable. One such example is taught by Dermer (Bio/Technology 1994 March 12; page 320) wherein Dermer teaches that data generated from cell lines

is not indicative of the cancer in humans. Another example, taught by Weiss (Washington Post 1998 May 6; A3) teaches that although effective and promising in mouse models, proteins used to combat cancer is ineffective in humans.

The amount of direction or guidance present and the presence or absence of working examples: The specification provides working examples that describe the transduction of cells to produce cytokines, such as IL-2, IL-4, GM-CSF, TNF-a, and M-CSF, wherein the cells are ovarian and glioma. The cytokines described, with the exception of M-CSF, are all cytokines that are secreted, and are not membrane associated. Nowhere in the specification does it describe the construction of or preparation of other cytokines that are associated with the outer membrane of a cell. Furthermore, the working examples have only enabled one of skill in the art how to use cells expressing M-CSF in the capacity that it is expressed naturally as a membrane associated protein and has not detailed or described how one would make such a protein, wherein the cytokine is expressed or is genetically modified to express a membrane associated protein. In addition, the working examples have not provided any guidance in the way of how cytokines expressed on the surface of the cell are to be used in treating neoplastic diseases. Because there is a lack of such information, concerning the linking or associating of cytokines to the surface of the cell and what effects it has immunologically, one of skill in the art would be forced to see what effects, detrimental or efficacious, the linking or associating of a cytokine would have on the immune system.

The breadth of the claims and the quantity of experimentation needed: Because the specification is limited in the disclosure of specific compositions, and because the status of the current art and because the instant specification has not described or explained the role and or effects of the instant composition, one of skill in the art would be forced into undue experimentation to determine how to make such compounds and if such compounds would be effective and functional.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 31-33,36-38,40,49,52,57,and 59-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimura *et al* (Exp Hematol 1996 Feb;24(2):360-3) (claims 31-33,36-38,40,49,52,57,and 59-62). Claims 31-33,36-38,40,49,52, 57 and 59-62 are drawn to a composition comprising a cell expressing a cytokine on the surface of the cell, wherein the cytokine is M-CSF and occurs naturally as a membrane cytokine, wherein the cell is a cancer cell, allogeneic, histocompatible, of the same tissue type as the tumor, and has been transduced by with a retroviral expression vector, wherein the composition further comprises a TAA, which is expressed on the same cell as the cytokine, and a method of producing a composition comprising a cell comprising transduction with an expression vector, wherein the vector is retroviral, wherein the

cytokine is a M-CSF and is expressed under the control of a promoter, wherein the cell is of the same cell type as the tumor, allogeneic, and histocompatible, and comprising transducing a cell with an expression vector expressing a cytokine on the surface of the cell and providing the cell in combination with a TAA.

Kimura *et al* teach a cellular composition comprising a surface expressed form of M-CSF, wherein in the absence of any evidence to the contrary, M-CSF is the naturally occurring transmembrane form, wherein the cell is a L1210 cell which is derived from a mouse tumor, allogenic because it is to be injected into a mouse, and in the absence of any evidence to the contrary is also histocompatible, the tumor formed is of the same tissue type as L1210 cell, and because the L1210 cell is derived from a cancerous tissue also inherently contains TAA which are expressed on the same cell as the expressed cytokine. Furthermore, Kimura *et al* also teach a method of producing a cell comprising a surface expressed cytokine, wherein the cytokine is M-CSF and is expressed under the control of a promoter, wherein the cell is allogeneic, and is provided in combination with a TAA.

11. Claims 31-33,35-37,40,49,52, and 54-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Jadus *et al* (Blood 1996 Jun 15;87(12):5232-41) (claims 31-33,35-37,40,49,52, and 54-62).

Jadus *et al* teach a composition and a method of making the composition which is a retrovirally transduced glioma cell which is driven by a promoter to express a naturally occurring surface form of M-CSF, wherein the cell expressing the cytokine is

allogeneic and histocompatible. Further, because Jadus *et al* use a glioma cell to express the cytokine, inherently it also expresses a TAA.

12. Claims 31-32, 52,55,57, and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Tuck *et al* (Blood 1994 Oct 1; 84(7):2182-8). Claims 31-32,36,52,55,57,59, and 61 are drawn to a composition comprising a cell expressing a cytokine on the surface of the cell, wherein the cytokine is M-CSF and wherein the cytokine naturally occurs as a membrane cytokine, and a method of producing a composition comprising transducing a cell with a cytokine which is to be expressed on the surface of the cell, wherein the cytokine produced is M-CSF and wherein the cytokine is produced under a promoter.

Tuck *et al* teach of a COS-1 cell expressing a M-CSF cytokine, wherein the cytokine is M-CSF and the M-CSF, which can be either membrane associated or soluble cytokine in its natural form, is membrane associated. Furthermore, Tuck *et al* also disclose of a method of producing a cell which expresses M-CSF on the surface of the cell, driven by an expression promoter.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
September 30, 2002

Brenda Brumback

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